REMARKS

Applicant has amended the claims in order to more particularly define the invention, and in consideration of the comments contained in the outstanding Official Action. Claim 1 has been amended to indicate that the ranitidine is present in an effective amount and to delete the objected to terminology "also containing." Claim 8 has been cancelled from the application as being redundant. Claims 10-11 have been cancelled from the application and replaced by claims 15-17 which depend from claim 1. All of the claims now present in the application (claims 1-3, 5-7 and 12-17) are believed to be in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

More particularly, the outstanding Official Action sets forth a rejection of claims 1-3 and 5-10 under 35 U.S.C. 112, second paragraph, for the inclusion of the phrase "also containing alcohol" in claim 1. Applicant has amended claim 1 to replace the objected to terminology with the language "comprising." Accordingly, it is respectfully requested that this aspect of the rejection be withdrawn.

The Official Action indicates that the claims should state how the pH is arrived at. This aspect of the rejection, having been carefully considered, is most respectfully traversed. Applicant respectfully submits that the specification clearly teaches that pH may be adjusted by the use of buffer salts but the specification is equally clear that this is only a preferred way of adjusting the pH. If the solution is prepared using ranitidine free base as input material, then the desired pH may be obtained by the addition of a physiologically acceptable acid such as hydrochloric acid. Alternatively, if the input material is ranitidine hydrochloride, then the desired pH may be obtained by addition of the required amount of a physiologically acceptable base such as sodium hydroxide. These possibilities would be immediately apparent to one of ordinary skill in this art. These possibilities also demonstrate the fact that the precise means by which the desired pH is adjusted is not an essential feature of the invention. Accordingly, it is respectfully requested that this aspect of the rejection be withdrawn.

Claims 1-3 and 5-12 stand rejected for failing to recite amounts of ingredients. Claim 1 has been amended to indicate that the ranitidine is present in an effective amount.

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In addition, claims 15-17 specifically recite amounts of ranitidine present. Accordingly, it is respectfully requested that this rejection be withdrawn.

All of the claims in the application stand rejected under 35 U.S.C. 103 as being unpatentable over the Chemical Abstracts citation. This reference is said to teach the cojoined use of ranitidine and an alcohol (ethanol). The various parameters of the claims, such as pH and amounts, are considered by the Official Action as choices to one of ordinary skill in the art. The Official Action concludes that such parameters have not been demonstrated as being critical and therefore they are considered to be within the skill of the art. This rejection, having been carefully considered, is most respectfully traversed.

At the outset, Applicant specifically traverses the statement in the Official Action that the references relied upon by the Examiner teach the cojoining of ranitidine and an alcohol, e.g., ethanol. Applicant most respectfully submits that the art does not teach the cojoining of ranitidine and an alcohol and pharmaceutical composition which is an aqueous formulation for oral administration. These references do not lead one of ordinary skill in the art in any way to expect that stability of ranitidine in an aqueous oral formulation could be enhanced by the presence of ethanol and does not suggest the presence of ethanol in such compositions.

The first Chemical Abstract reference (97, 61014G) relates to a new polymorphic form of ranitidine hydrochloride (designated form 2) and includes a description of processes for its production. Applicant most respectfully submits that all that one of ordinary skill in the art would be able to infer from this reference is that ranitidine hydrochloride must be reasonably stable in ethanol since ethanol is used as a solvent for recrystallization. However, there is no teaching whatever that the stability of ranitidine or its salts as an aqueous formulation for oral administration is enhanced by the presence of ethanol and there is no suggestion that ethanol should be included in pharmaceutical formulations containing ranitidine as presently claimed.

The second Chemical Abstracts reference (104 102280Z) relates to a paper in a Scandinavian journal indicating that the presence of ethanol in a person's diet did not

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adversely affect the gastric acid secretion inhibiting properties of ranitidine. Again, there is absolutely no teaching in this reference that would lead one of ordinary skill in the art to expect that ethanol would enhance the stability of ranitidine in aqueous oral formulations or would suggest to one of ordinary skill in the art that ethanol should be added to such formulations.

In summary, the prior art relied upon in the rejection is, in fact, extremely far removed from the presently claimed invention and in no way renders it obvious. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicant wishes to reiterate that the stability of a pharmaceutical formulation for oral administration is the most important factor, and enhancing the stability of the active ingredients of such formulations is always an objective. Thus, in the development of any pharmaceutical formulation, it is necessary to ensure that the drug substance is stable within the formulation, which is necessary for two main reasons. Firstly, the drug substance must be stable in order to ensure that the patient is receiving the correct dosage of the drug. Secondly, it is important to ensure that the patient is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This second point is particularly important since it is not always possible to identify fully all of the breakdown products that may occur. Consequently, the chronic toxicity of all the various compounds arising from the breakdown of the drug substance cannot be determined.

In practice, degradation of the drug substance within a formulation usually occurs upon storage and is often dependent upon a number of factors including temperature and time of storage. Any improvement that can be made in enhancing the stability of the drug substance can only benefit the patient since it ensures more accurate dosage and the intake of less breakdown products. In addition, enhancement of the stability of the drug substance also benefits from the economic point of view in that it increases the effective shelf life of the product. There is not even the most remote suggestion of this in the prior art of record.

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Applicant is in the process of preparing a Declaration to substantiate the unexpected effect of ethanol in enhancing the stability of ranitidine in aqueous oral formulations. However, Applicant does not believe that the Declaration will be available for filing at the Patent Office for another six weeks. Applicant is making every effort to expedite preparation of the Declaration; however, due to circumstances beyond the control of the Applicant, there have been unexpected delays in obtaining the executed Declaration.

Applicant at this time wishes to direct the attention of the Examiner to additional information which may be material to the prosecution of the present application. This information is listed on attached form PTO-1449 and copy of each will be submitted to the Examiner as soon as copies are available.

Both of the listed publications were cited in connection with the corresonding applications in France and Belgium. FR-A-2,547,727 is another equivalent to GB-A-2,142,820 (of record).

French application 2,501,206 relates to novel compounds which are structurally different from ranitidine. Inasmuch as it discloses pharmaceutical formulations, this reference refers only to prior art formulation techniques and applies these to the novel compounds which are disclosed. There is no teaching in this reference whatever that the stability of ranitidine in aqueous solution (or indeed the stability of the novel compounds with which the reference is concerned) can be enhanced by the addition of ethanol.

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In view of the above comments and amendments to the claims, favorable reconsideration and allowance of all claims now present in the application are believed to be in order and are most respectfully requested.

Respectfully submitted,

Richard E. Fichter

RICHARD E. FICHTER
Registration No. 26,382

Date: October 31, 1990

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LO494804

#12
JRL
11/21/90

Sheet 1 of 1

FORM PTO-1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
REF/Long/804	07/494,804
APPLICANT: David R. LONG	
FILING DATE: 03/14/90	GROUP: 125

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
DG		FR-A-2,547,727	12/84	France	~~A61K~~	~~31/64~~		
DG		GB-A-2,142,820	1/85	Great Britain	~~A61K~~	~~31/59~~		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER: Juliette CHEVALIER

DATE CONSIDERED: 1-17-91

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(12) UK Patent Application (19) GB (11) 2 142 820 A

(43) Application published 30 Jan 1985

(21) Application No 8412108

(22) Date of filing 11 May 1984

(30) Priority data
(31) 8313217 (32) 13 May 1983 (33) GB

(51) INT CL³
A61K 31/34

(52) Domestic classification
A5B 180 444 446 44Y 451 45Y 540 54Y 565 56Y 823 H L N
U1S 1318 A5E

(56) Documents cited
None

(58) Field of search
A5B

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(54) Aqueous compositions of ranitidine

(57) Aqueous formulations of raniditine have been found to have enhanced shelf life provided that they are formulated with a pH in the range 6.5–7.5. Suitable aqueous formulations include injections for intravenous and intramuscular administration, continuous infusions and oral preparations such as syrups.

GB 2 142 820 A

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SPECIFICATION

Pharmaceutical compositions

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H_2 antagonist ranitidine.

Ranitidine [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethene-diamine] and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous administration and another of an oral syrup. Both of these formulations contain sufficient hydrochloric acid to achieve a pH of 5.0. In addition injection formulations are described by Padfield et al (The Chemical Use of Ranitidine, Medicine Publishing Foundation Symposium Series 5, Oxford:Medicine Publishing Formulation 1982 pp 18–22) in the form of a simple aqueous solution of ranitidine hydrochloride at is natural pH, i.e. about 5.5. Whilst such formulations containing ranitidine and/or its physiologically acceptable salts are therapeutically effective they suffer from the disadvantage of having a relatively short shelf life due to the breakdown of the ranitidine.

We have now surprisingly found that the shelf life of aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts may be significantly enhanced if the pH of the formulation is adjusted within the range of 6.5–7.5.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salt thereof, having a pH within the range of 6.5–7.5. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients.

The aqueous based ranitidine formulations according to the invention are particularly stable when compared with formulations at a lower pH. Thus for example, in the case of a 25 mg/ml ranitidine hydrochloride injection solution buffered to the appropriate pH with phosphate salts and subjected to storage at 20°C, the rate of breakdown of the ranitidine is about ten times faster for a solution buffered to pH 5.5 than for a solution buffered to pH 7.0.

Conveniently the pH of the formulation according to the invention is adjusted on manufacture within the range 6.5–7.5 by means of the use of suitable buffer salts, for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

Preferred formulations according to the invention are those wherein the pH is within the range 6.7 to 7.3, for example 6.8 to 7.1.

A preferred embodiment of the invention is an aqueous formulation for parenteral administration. Such a formulation may comprise water suitable for injections in which is dissolved ranitidine and/or one or more of its physiologically acceptable salts and suitable buffer salts. Preferably the solution is adjusted to tonicity by the addition of the appropriate conventional excipients e.g. sodium chloride. Optionally the composition may also contain an antimicrobial preservative, for example phenol.

The concentration of ranitidine in formulations suitable for injection, e.g. intravenous or intramuscular injection is conveniently within the range 10–100 mg/ml, for example 25 mg/ml, expressed as free base. If desired, the solution may be diluted prior to use with, for example, an isotonic saline solution or a dextrose solution. Solutions suitable for continuous infusion may have a concentration of ranitidine of 0.1–2.0 mg/ml, preferably 0.5–1.0 mg/ml, expressed as free base. The solutions for continuous infusion may be presented in this form, for example in packs of 50–100 ml, or may be presented in a more concentrated form, i.e. 10–100 mg/ml, e.g. 25 mg/ml, for subsequent dilution before use, with, for example, an isotonic saline solution or a dextrose solution.

The aqueous formulations for parenteral administration are conveniently prepared by dissolving ranitidine and/or one or more of its physiologically acceptable salts and the excipients in water suitable for injections. The solution, which conveniently is sparged with an inert gas such as nitrogen, is sterilised preferably by filtration and then aseptically packed into suitable containers, e.g. ampoules, vials or containers for infusion, under an atmosphere of nitrogen. Alternatively the formulation may be terminally sterilized, for example by heating.

A further preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, together with buffer salts, a preservative and a viscosity enhancing agent. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.

Suitable buffer salts for the oral formulation include potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol, glycerol,

sucrose or a cellulose derivative such as carboxymethyl cellulose or an ether thereof such as an alkyl and/or a hydroxyalkyl ether of cellulose as for example hydroxypropyl methyl-cellulose.

Suitable preservatives include the alkyl hydroxybenzoates, such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

Suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

The concentration of ranitidine in the oral formulation, expressed as free base is conveniently within the range of 20–400 mg per 10 ml, for example 20–200 mg per 10 ml, more particularly 150 mg per 10 ml dose.

The aqueous formulations for oral administration are conveniently prepared by adding an aqueous solution of ranitidine and/or one or more of its salts together with the other excipients to an aqueous solution or dispersion of the viscosity enhancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

Illustrative examples of formulations according to the invention are as follows. In these examples the relative proportions of ranitidine hydrochloride and buffer salts are such that each formulation has a pH of approximately 7.

Raniditine Injection for Intravenous administration (25 mg/ml)

Example 1	mg/ml
Ranitidine hydrochloride	28
Potassium dihydrogen orthophosphate	0.96
Disodium hydrogen orthophosphate, anhydrous	2.4
Phenol BP	5
Water Suitable for Injections BP to	1 ml

Ranitidine hydrochloride, the buffer salts and the phenol were dissolved in Water for Injection. The solution was sparged with nitrogen, sterilised by filtration and then aseptically packed into vials under an atmosphere of nitrogen and sealed with a suitable closure.

Example 2	mg/ml
Ranitidine hydrochloride	28
Potassium dihydrogen orthophosphate	0.96
Disodium hydrogen orthophosphate, anhydrous	2.4
Sodium chloride BP	1.6
Water Suitable for Injections BP to	1 ml

An aqueous solution of the ranitidine hydrochloride, the buffer salts and sodium chloride was prepared using Water for Injection. The solution was sparged with nitrogen, sterilised by filtration and then aseptically packed into ampoules under an atmosphere of nitrogen.

Ranitidine oral liquid formulation (150 mg/10 ml)

Example 3

	% w/v
Ranitidine hydrochloride	1.68
Hydroxypropyl methylcellulose	q.s.
Parabens (preservative)	q.s.
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate, anhydrous	0.350
Sweetening agent(s)	q.s.
Flavour	q.s.
Purified Water BP to	100 ml

A solution of the ranitidine hydrochloride together with the other excipients, except hydroxypropyl methylcellulose, in purified water was added with mixing to a dispersion of the hydroxypropyl methylcellulose in purified water.

Ranitidine formulations for intravenous infusion.

	Example 4 For a 50 ml Infusion mg/ml	Example 5 For a 100 ml Infusion mg/ml
Ranitidine hydrochloride	1.12	0.56
Citric acid BP	0.3	0.3
Disodium hydrogen orthophosphate, anhydrous	1.8	1.8
Sodium chloride BP	4.5	4.5
Water Suitable for Injections BP	to 50.0 ml	to 100.0 ml

An aqueous solution of the ranitidine hydrochloride, the buffer salts and the sodium chloride is prepared using Water for Injections. The solution is sparged with nitrogen, filled into containers suitable for administering the solution by intravenous infusion, and sterilised by autoclaving.

CLAIMS

1. A pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof, the formulation having a pH within the range 6.5–7.5.
2. A pharmaceutical composition as claimed in claim 1 having a pH in the range 6.7 to 7.3.
3. A pharmaceutical composition as claimed in claim 1 having a pH in the range 6.8 to 7.1.
4. A pharmaceutical composition as claimed in any of claims 1 to 3 in which the pH is adjusted by means of suitable buffer salts.
5. A pharmaceutical composition as claimed in claim 4 in which the buffer salts are potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.
6. A pharmaceutical composition as claimed in any of claims 1 to 5 in a form suitable for parenteral administration.
7. A pharmaceutical composition as claimed in claim 6 in a form suitable for injection and containing 10 to 100 mg/ml ranitidine, expressed as free base.
8. A pharmaceutical composition as claimed in claim 6 in a form suitable for continuous infusion and containing 0.1–2.0 mg/ml ranitidine, expressed as free base.

9. A pharmaceutical composition as claimed in any of claims 1 to 5 in a form suitable for oral administration.

10. A pharmaceutical composition as claimed in claim 9 containing 20–400 mg per 10 ml dose.

11. A pharmaceutical composition as claimed in any of claims 1 to 10, containing ranitidine in the form of its hydrochloride salt.

12. A process for the production of a pharmaceutical composition as claimed in any of claims 1 to 11 which comprises processing the various components to provide an aqueous formulation suitable for administration to patients.

13. A process as claimed in claim 12 for the production of a composition suitable for parenteral administration, which comprises dissolving ranitidine and/or one or more physiologically acceptable salts thereof and the remaining constituents in water suitable for injection, followed by sterilisation.

14. A process as claimed in claim 12 for the production of a composition suitable for oral administration which comprises adding an aqueous solution of ranitidine and/or one or more physiologically acceptable salts thereof to an aqueous solution or dispersion of a viscosity enhancing agent.

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Law

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/494,804 03/14/90 LONG D

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GARDNER, D

125 14

01/22/91

☒ This application has been examined ☒ Responsive to communication filed on 1-10-91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3, 5-7, 12-17 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 5-7, 12-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTOL-326 (Rev. 9-88) EXAMINER'S ACTION

The following Office Action is a result of the telephone conversation conducted between Richard Fichter and myself on 1/17/91. Claims 1-3, 5-7 and 12-17 are pending at this time.

Rejections presented by Examiner Friedman in the Office Action dated 5/4/90 are deemed to be overcome by the amendment filed on 10/31/90.

However, new rejections must now be presented as a result of the additional documents which were filed on 1/10/91.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country,

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or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-7 and 12-17 are rejected under 35 U.S.C. § 102(a) and (b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Padfield et al. (GB 2142820). Padfield et al. teach the enhanced stability of aqueous compositions of ranitidine formulated at a pH in the range of 6.5 to 7.5. The applicant's invention is directed to aqueous compositions of ranitidine formulated at a pH in the rage of 6.5 to 7.5 and with the addition of ethanol. It has not been demonstrated in the record, by means of experimental data, that the applicant's invention produces any unexpected results. The disclosure, as presented, is insufficient to overcome the prior art without the aid of experimental data to show a definite improvement over the GB patent. Since the GB patent teaches an aqueous composition of ranitidine, it is considered well within the state of the art to choose ethanol as an additive which would be considered pharmaceutically acceptable when formulating this composition. Absent evidence to the contrary, the addition of ethanol is considered merely to be a choice among known conventional excipients.

No claims area allowed.

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It is noted that the amendment dated 10/31/90 stated that a new Declaration was in the process of being prepared. This paper has not yet been received.

Any inquiry concerning this communication should be directed to Diane Gardner at telephone number (703) 308-3727.

FREDERICK E. WADDELL
EXAMINER
GROUP ART UNIT 125

Diane Gardner
January 17, 1990

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
David R. LONG : Examiner: Gardner
Serial No.: 07/494,804 : Group Art Unit: 125
Filed: March 14, 1990 :
For: PHARMACEUTICAL COMPOSITIONS :

REQUEST FOR RECONSIDERATION

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

This is in response to the Official Action dated January 22, 1991, the period for response to which has been extended to expire on May 22, 1991, by the filing herewith of a petition for a one month extension of time and payment of the required fee.

The outstanding Official Action sets forth a rejection of all of the claims under 35 U.S.C. §102(a) and (b) as anticipated by, or, in the alternative, under 35 U.S.C. §103 as obvious over Padfield et al. (Great Britain 2142820). The Official Action maintains that the Padfield et al. publication teaches the enhanced stability of aqueous compositions of ranitidine formulated at a pH in the range of 6.5 to 7.5. Applicant's invention is directed to aqueous compositions of ranitidine formulated at a pH in the range of 6.5 to 7.5 with the addition of ethanol.

The Official Action urges that it has not been demonstrated in the record by means of experimental data that Applicant's invention produces any unexpected results. In addition, it is stated that, absent evidence to the contrary, the addition of

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ethanol is considered merely to be a choice among known conventional excipients. These rejections, having been carefully considered, are most respectfully traversed.

Applicant submits herewith a Declaration of Dr. John Hempenstall which provides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 in terms of the stability of the ranitidine in the composition. In this connection, it is noted that the liquid formulation without ethanol which is used in the Declaration for purposes of comparison is the same as the formulation of Example 3 of Padfield et al. Accordingly, the Declaration presents a direct comparison between a composition according to the present invention and a composition according to the prior art.

The Official Action bases the rejection of the present application under 35 U.S.C. §103 on a statement that the use of ethanol is considered merely to be a choice among known conventional excipients. Applicant acknowledges that ethanol has previously been used in pharmaceutical compositions. However, the purpose for which ethanol has been included has been either as a solvent or as a preservative against bacterial contamination. There was, however, no reason to suppose that either of these functions of ethanol would have had any beneficial effects in terms of limiting the degradation of ranitidine in aqueous formulations thereof.

For this reason, there would have been no motivation whatever for one of ordinary skill in the art to include ethanol in an aqueous ranitidine formulation. Ranitidine is very soluble in water and ethanol is quite unnecessary to assist in the dissolution of ranitidine in the formulation. In addition, other and better preservatives are available.

Furthermore, there is a clear disincentive against the use of ethanol in aqueous formulations. Thus, an important use of ranitidine is in the treatment of peptic ulcers and related conditions, and it is well known that alcohol (i.e., ethanol) can aggravate such conditions. In fact, the amount of ethanol required for use according to the present invention is at such a low level that no adverse effects are observed as a result of the presence of ethanol, but fairly clear and beneficial effects on drug stability are evident.

However, the fact that ethanol has a known effect in aggravating one of the main conditions that the compositions according to the invention are intended to treat would be a clear disincentive to including ethanol without knowledge of the beneficial effects on stability. This knowledge is, of course, provided only by the present invention. Thus, there was no motivation whatever for one of ordinary skill in the art to include ethanol in aqueous ranitidine formulations and the beneficial effects obtained by the use of ethanol were most definitely unexpected.

Applicant notes that a claim for priority of United Kingdom Application No. 8629781 was made in the Declaration of the grandparent application Serial No. 07/131,442, and a certified copy of the priority document was filed in the grandparent application. Accordingly, it is most respectfully requested that the Examiner acknowledge the claim for priority and the filing of the priority document in the next Official Action in the present application.

In view of the above comments and of the submission of the Declaration of Dr. Hempenstall, favorable reconsideration and allowance of all claims now present in the application are believed to be in order and are most respectfully requested.

Respectfully submitted,

Richard E. Fichter

Richard E. Fichter
Registration No. 26,382

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REF/er

Date: May 10, 1991

LO494804.A2

#11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
David R Long

Serial No. 07/494804 Group Art Unit: 125

Filed: 14 March 1990 Examiner Gardner

For: PHARMACEUTICAL COMPOSITION

DECLARATION

I, JOHN HEMPENSTALL, A British subject and a resident of 49 Seymour Road, St. Albans, Hertfordshire, England, do hereby declare as follows:-

1. I am a Research Leader in the Pharmacy Division of Glaxo Group Research Limited, a subsidiary of Glaxo Group Limited.

2. I obtained the degree of Bachelor of Science (Pharmacy), with honours, in 1977 at the University of Aston in Birmingham and a Doctorate in Pharmaceutical Sciences at the same University in 1982. I am a member of the Royal Pharmaceutical Society of Great Britain. I joined the Pharmacy Division of Glaxo Group Research in 1982 and was appointed to my present position in 1988.

3. Ranitidine is a highly effective therapeutic agent in man for the treatment of gastric and duodenal ulcers. It is administered to the patient in several forms including parenteral and oral administration.

4. In the development of any pharmaceutical presentation it is necessary to ensure that the drug substance is stable within the formulation for as long a time period as is practical, so that the

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patient is receiving the correct dosage and also that he or she is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This latter point is particularly important since it is not always possible to fully identify all the breakdown products that can occur and consequently one cannot determine the chronic toxicity of all the various compounds arising from the breakdown of the drug substance.

5. In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and surprising enhancement in the stability of the ranitidine is achieved by the addition of ethanol to the formulation. The advantageous effect resulting from the addition of ethanol to an aqueous based ranitidine formulation can readily be determined by comparing the stability of the ranitidine in a formulation according to the present invention and the same formulation but without the added ethanol.

6. In US Serial No. 07/494804 there is provided an example of a typical ranitidine oral liquid formulation according to the invention.

Stability studies were carried out comparing this formulation with a formulation that was identical except that it did not contain ethanol. Samples of each formulation were stored at 30^0C, 37^0C and 45^0C for approximately 3 years and the ranitidine content measured by high performance liquid chromatography (h.p.l.c.) against a standard, which was the corresponding formulations stored at 4^0C. At each temperature 2 samples of the formulation without ethanol, identified as Batches 1 and 2 were analysed along with 3 samples of the formulation with ethanol identified as Batches 3, 4 and 5. The specific formulations used in the study were as follows:-

Ranitidine oral liquid formulation (150mg/10ml expressed as free base)

	With Ethanol % w/v	Without Ethanol % w/v
Ranitidine hydrochloride	1.68	1.68
Ethanol	7.5	
Potassium dihydrogen orthophosphate	0095	0.095
Disodium hydrogen orthophosphate anhydrous	0.350	0.350
Hydroxypropylmethylcellulose	qs	qs
Preservative	qs	qs
Sweetening agents	qs	qs
Flavour	qs	qs
Purified water BP to	100ml	100ml

The acceptable shelf life for an aqueous formulation containing ranitidine hydrochloride is considered to be the time at which no more than 5% of the ranitidine present in the formulation has degraded. Accordingly, the figure determined from the stability studies was the time (in months) for 5% ranitidine loss calculated as the lower 95% confidence limit. The results are as follows:

	Without Ethanol		With 7.5% Ethanol		
Temperature	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
30^0C	12.5	13.6	19.5	17.0	20.8
37^0C	5.4	4.7	7.8	7.1	7.5
45^0C	1.8	2.3	2.9	2.9	2.8

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Thus the formulation with ethanol has an average shelf life at 30^0C of 19 months compared with 13 months when ethanol is excluded from the formulation. This is a highly significant and valuable improvement.

The stability of oral liquid formulations as described above except containing varying amounts of ethanol was also studied at 37^0C and 45^0C. The clear advantageous effects of the presence of ethanol can be seen from the following table which gives the time (in months) for 5% ranitidine loss (calculated as the lower 95% confidence limit).

Temperature	% Ethanol				
	0	2.5	5.0	7.5	10.0
37^0C	5.9	7.2	7.6	7.7	6.4
45^0C	2.1	2.4	2.4	2.6	2.7

7. The above results clearly show that ethanol has a beneficial effect upon the stability of ranitidine in aqueous based formulations and furthermore I am not aware of any teaching in the art that would lead me to expect such an effect.

8. I declare further that all statements made herein to my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that each wilful false statement may jeopardise the validity of the application or any patent issuing thereon.

JOHN HEMPENSTALL

Date: 12th April 1991

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